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Assessment of Antiviral combination therapy with Cephalosporin antibiotic for prevention of severe Influenza-A (H1N1)pdm09 infection associated secondary bacterial infection and other complications

Azfar Athar Ishaqui[1,2,3], Amer Hayat Khan[1*], Syed Azhar Syed Sulaiman[1], Muhammad Alsultan[2,3] and Irfanullah Khan[1]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia
[2]Department of Pharmacy, King Abdulaziz Hospital, Ministry of National Guard Health – Health Affairs, Alahsa, Saudi Arabia
[3]King Abdullah International Medical Research Center, Alahsa, Saudi Arabia

Abstract: Secondary bacterial infection is considered as a major complication associated with severe Influenza-A (H1N1)pdm09 infection responsible for the mortalities and morbidities worldwide. Use of antibiotics in viral Influenza infection is still debatable. All the confirmed diagnosed hospitalized Influenza-A (H1N1)pdm09 infection patients fulfilling inclusion/exclusion criteria during the study period were divided into two groups based on drug therapy for initial 72 hours. Group-1 included those patients who received oral oseltamivir alone while Group-2 included patients who were initiated on oseltamivir in combination with empiric cephalosporin antibiotic within 6-8 hours after hospitalization. The patients of both groups were assessed for incidences of various complication associated with Influenza-A (H1N1)pdm09 infection. A total of 227 and 116 patients were enrolled for Group-1 and Group-2 respectively. The incidences of secondary bacterial infections were significantly less ($P<0.05$). Moreover, length of stay in hospitalization, need of ICU admission, multiple organ failure and need of respiratory support were also significantly less ($P<0.05$) for Group-2 patients. Majority of patients that suffered complications were unvaccinated and aged more than 50 years with multiple comorbidities. Among cephalosporins, cefuroxime was found to be least effective in prevention of Influenza associated complications. Early initiation of empiric antibiotic therapy in combination with oseltamivir can prevent complications associated with Influenza-A (H1N1)pdm09 infection especially in elderly and unvaccinated high risk patients. Different combinations of antibiotics and antiviral medications need to be analysed for the prevention of severe Influenza infection complications.

Keywords: Secondary bacterial infections, oseltamivir, cephalosporin, influenza a (H1N1)pdm09, complications of influenza infection.

INTRODUCTION

Infectious diseases are considered to be second most cause of deaths around the globe after cardiovascular diseases (Davey, 1999). Acute respiratory infections accounts for around 30% of deaths caused by infectious diseases. Combined infections are largely understudied and considered to be most difficult scenarios in terms of treatment (Pasman, 2012). Secondary infections are those infections which occur during hospitalization for when patient is admitted for treatment of primary infection (Purcell and Fergie, 2004). Secondary infections are common in Influenza affected hospitalized patients. The prevalent co-infecting organisms are *Streptococcus pneumoniae* followed by *Staphylococcus aureus*, but several other organisms are also reported to cause infections (Klein, Monteforte *et al*., 2016). Influenza and bacterial co-infection give rise to substantial morbidity and mortality (Chertow and Memoli, 2013).

Early diagnosis of bacterial co-infections in Influenza-A (H1N1)pdm09 affected patient is challenging, because of the various coinciding symptoms and the absence of particular clinical indications of bacterial co-infections associated with Influenza-A (H1N1)pdm09 infection alone (Libster, Bugna *et al*., 2010). The British Thoracic Society recommends a beta lactamase stable penicillin or second/third generation cephalosporin together with a macrolide in adults with severe Influenza related pneumonia (Lim, 2007). However, misuse of antibiotic causes antibiotic-resistance, antibiotic-associated infections, increased costs and adverse events, ranging in severity from mild (e.g. diarrhoea and rash) to life-threatening (e.g. Stevens–Johnson syndrome and anaphylaxis) (Engelmann, Dubos *et al*., 2015). Providers should consider possible bacterial co-infection in patients hospitalized with Influenza, and bacterial cultures should be taken to avoid patient exposure to the risks of prolonged unnecessary antibiotic use (Klein, Monteforte *et al*., 2016).

There is a paucity of evidence on which to base the use of empiric antibiotics in the setting of Influenza, and this is reflected in the recommendations around their use during pandemics and interpandemic periods (Campigotto and Mubareka, 2015). Based in part upon post-mortem

**Corresponding author:* e-mail: dramer@usm.my

findings of bacterial pneumonia during the 2009 pandemic, the Infectious Diseases Society of America suggests treatment with cephalosporins and a macrolide for critically ill individuals with suspected bacterial pneumonia; individuals for whom Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia is a possibility (critically ill, cavitary lesion or necrosis on chest radiography, Gram-positive cocci in clusters noted on respiratory specimens or evidence of empyema) should receive Vancomycin or Linezolid (America, Ng, Narasaraju *et al*., 2012). Neuraminidase inhibitors in combination with antibiotics, on the other hand, can facilitate recovery from Influenza and alter the co-infection pathogenesis (Smith and McCullers, 2014). The current study aims to assess early initiation of Cephalosporin antibiotic in combination with antiviral drug (Oseltamivir) for prevention of secondary bacterial infections and other associated complications in severe Influenza-A (H1N1)pdm09 infection hospitalized patients.

MATERIALS AND METHODS

Study settings

This study was conducted in state-owned tertiary care health facilities (Riyadh & Alahsa region, Saudi Arabia) responsible to provide healthcare services to current and retired military personnel along their family members and hospital staff.

Study duration

This cohort study was conducted during period of three years i.e. January, 2016 to October, 2019.

Study design

All the patients who came to emergency department during the study with Influenza like illness during the Influenza season were examined for presence of Influenza virus via reverse transcriptase polymerase chain reaction (RT-PCR) technique for qualitative detection of Influenza-A, Influenza-B and Influenza-A (subtype 2009 H1N1). A clinical specimen of nasal swab, tracheal swab, nasopharyngeal swab or buccal swab of patients was used for this purpose. Only patients with confirmed diagnosis of Influenza-A (H1N1)pdm09 with severe illness symptoms who required hospital admission were enrolled in the study. All the Influenza admitted patients were kept in isolation room. Patients with Influenza A (non-H1N1) and Influenza B patients were excluded.

For all the confirmed diagnosed Influenza patients of Influenza-A (H1N1)pdm09, patients were divided into two groups on the basis drug treatment received during hospitalization for the treatment of Influenza infection. Group-1 includes those patients who were initiated on antiviral drug (Oseltamivir) alone within 6-8 hours of hospital admission. Group-2 comprises those patients that were primarily initiated on oral antiviral drug (Oseltamivir) in combination with empirically prescribed antibiotic from cephalosporin group within 6-8 hours of hospital admission. For both group patients, oseltamivir was initiated at an oral dose of 75mg twice a day daily for 5 days in patients with Glomerular filtration rate (GFR) more than 60ml/min. For patients with acute kidney injury having GFR >30 to 60 mL/min, oseltamivir was initiated at 30 mg twice daily while patients with GFR >10 to 30 mL/min at a dose of 30 mg once daily.

For the enrolled patients in both groups, a sepsis work-up (blood and urine cultures), pneumonia work-up (radiological examination i.e., chest x-ray, computerized tomography (CT) scan of lungs or chest ultrasound) and meningitis work-up was done for patients who were presented with neurologic complications in emergency department. Secondary bacterial infections are those infections which occur during hospitalization when patient is admitted for treatment of primary infection i.e Influenza-A (H1NI) in current study (Purcell and Fergie, 2002).

The decision of initiating the Group-2 patients on empiric antibiotic was solely taken by team of clinicians mostly headed by Infectious disease consultant based on suspecting any secondary bacterial infection associated with Influenza infection. Among cephalosporins, the patients who were given intravenous Cefuroxime (1.5gm every 8 hourly), ceftriaxone (2gm every 24 hourly) and cefepime (1gm every 8 hourly) as empiric therapy in combination with antiviral (oseltamivir) were included in Group-2.

As per hospital protocol, different haematological laboratory parameters (white blood cell count, red blood cell count, neutrophils count and lymphocyte counts) and biochemistry laboratory parameters (sodium, potassium, urea and serum creatinine level) were monitored for all the patients. Moreover, the patients were also observed time to time for need of respiratory support and Intensive Care Unit (ICU) admission in case of severity of infection.

Inclusion criteria

- Adults, including pregnant and breast feeding women.
- Group-1; Patients who have been initiated on oral Oseltamivir therapy within 6-8 hours after Influenza infection detection and no antibiotic was initiated for atleast 72 hours after hospitalization.
- Group-2; Patients who were initiated on Cephalosporins (Cefuroxime, Ceftriaxone, Cefepime) together with antiviral (Oseltamivir) drug within 6-8 hours after Influenza infection detection and received this combination therapy for at least initial 72 hours.
- Patients that had not taken any antibiotic(s) either prescribed empirically or therapeutically in last 10 days.

- Patient with comorbid illnesses i.e., respiratory, cardiovascular, renal, diabetes etc.

Exclusion criteria

- Patients less than 18 years old or weight less than 40 kg.
- Patients discharged within 72 hours after hospitalization.
- Patients who tested negative for Influenza-A (H1N1)pdm09 infection on polymerase chain reaction assay testing (PCR testing) were excluded from the study.
- Presence of reported significant medical condition of ongoing malignancy.
- Known allergy to oseltamivir and prescribed antibiotic
- Patients having incomplete laboratory findings as needed for defined protocol.
- Patients who were initiated on empirically prescribed antibiotic other than Cephalosporin class of antibiotics (Group-2 only).

STATISTICAL ANALYSIS

All the statistical analysis was done by using SPSS (version 23.0) and Graphpad Prism (version 5.0). Continuous variables such as age, weight, length of hospital stay, no. of days on respiratory support and no. of days in ICU stay are presented as mean and Standard deviation. Chi-square test and unpaired t-test was used to evaluate univariate analysis. Statistical significance was established at P-value <0.05 considered as statistically significant.

Ethical approval

The study was approved by King Abdullah Medical & Research Center, King Abdulaziz Hospital, Alahsa (RYD-18-417780-131817) and patient confidentiality was maintained at all times.

RESULTS

A total of 589 patients were admitted in the hospital due to principal diagnosis of Influenza-A (H1N1)pdm09 during study period. All these patients were observed for the treatment initiated for treatment of Influenza infection. As per study protocol, these 589 patients were divided into two groups. Group-1 comprises 241 patients who were initiated on antiviral drug (Oseltamivir) only without any empirically prescribed antibiotic while Group-2 includes 225 patients who were given combination therapy of antiviral drug (Oseltamivir) in combination with empirically prescribed antibiotic. After thoroughly examining the patients according to inclusion criteria as per above defined protocol, a total of 227 and 116 patients were enrolled in the study for Group-1 and Group-2 respectively.

No statistical significant difference (P>0.05) was found among the enrolled patients for both groups in terms of male patients. Around 13 (9.2%) patients from total enrolled female participants were pregnant at the time of study. Average age of study participants for both groups was also statistically non-significant (P>0.05). Most of the participants from both groups' were unvaccinated for Influenza vaccine for that current season. Similarly, a very small proportion of participants i.e, 37 (10.8%) enrolled patients from both groups were found to be vaccinated with Pneumococcal vaccine. Among comorbidities, asthma and hypertension were found to be most common between both groups' enrolled patients. At the time of admission, different haematological and biochemistry laboratory parameters for patients both groups found to be statistically non-significant. Assessments of different characteristics of patients of both groups are summarized in table 1.

Table 2 shows summarized comparison of different clinical outcomes between both treatment groups. Patients belonging to combination treatment group of antiviral drug & Cephalosporin antibiotic showed statistically significant less incidences (P<0.05) of secondary bacterial infections with 12 (10.3%) patients as compared to 53 (23.4%) Group-1 patients. Microbiological profile of bacterial isolates identified by critical assessment of blood culture for recognized secondary infections are summarized in Table 3 which shows that secondary bacterial infections caused by different Gram positive cocci were dominant in both groups. The length of stay in hospital was also statistically less (P<0.05) for Group-2 patients with an overall average of 5.43±1.23 days as compared to 6.58±2.09 days for Group-1 patients. The patients whom required respiratory support during hospitalization were significantly less (P < 0.05) for Group-2 as compared to Group-1 patients. Moreover, the duration of respiratory support needed by patients was also statistically less (P<0.05) for combination treatment group with 3.6 ± 1.21 days. Also, the no. of patients requiring ICU admission due to worsening of clinical condition was statistically significant less (P < 0.05) for Group-2 patients. Moreover, the incidences of multi-organ failure was also found to statistically significant less for Group-2 patients (P < 0.05).

Table 4 represents the characteristics of patients suffered from secondary bacterial infection which shows that majority of patients from both groups that suffered from secondary infections were aged > 50 years. Similarly, majority of patients were also found be unvaccinated for pneumococcal vaccination as well as Influenza seasonal vaccination. Among incidences of secondary bacterial infections, a statistically significant difference was found for bacterial pneumonia infections with 38 (62.3%) and 6 (31.2%) patients for Group-1 and Group-2 respectively.

Various comorbidities such as obesity, renal insufficiency, chronic respiratory tract illness and diabetes were also found to be associated factors for severity of Influenza infection illness and found to be more prominent in patients suffered with complication of secondary bacterial infections in both group patients.

The three Cephalosporin antibiotics which were mainly prescribed empirically as a part of combination therapy for Group-2 patients are Cefuroxime (second generation Cephalosporin), Ceftriaxone (third generation Cephalosporin) and Cefepime (fourth generation Cephalosporin). The most commonly prescribed Cephalosporin in combination with Oseltamivir was Ceftriaxone. The incidences of secondary infections found to be less commonly occurred with Ceftriaxone as compared to Cefuroxime and Cefepime. Table 5 shows the summarized comparison of efficacy of Cefuroxime, Ceftriaxone and Cefepime of Group-2 patients.

DISCUSSION

This is very common in elderly patients to have diminished basic lung physiology along with immune system changes which predispose elderly people to less capacity to counter bacterial infections in the lungs (Chong and Street, 2008, Janssens and Krause, 2004). Considering the increased impact of mortality and morbidity associated with pneumonia infections specifically in elderly patients, the pneumococcal and Influenza vaccinations remains only viable option for the prevention of infection which still is amongst the most common cause of death by infectious diseases amongst elderly patients (Stupka, Mortensen *et al*., 2009). But it was shown in current study that underuse of pneumococcal and Influenza vaccinations resulted in increased complications associated with severe Influenza-A (H1N1)pdm09 infection. It is also evident from current study that Group-2 patients underwent fewer complications as compare to Group-1 patients because of early initiation of antibiotic together with initiation of Oseltamivir which not only reduces the frequency of patients suffered from bacterial pneumonia as secondary infection but also helpful from early recovery from severe disease illness and prevention of other complications such as multiple organ failure which indirectly associated with need of respiratory support and need of ICU admission.

Streptococcus pneumoniae which is found to be the most common pathogen associated with secondary infections was reported to be susceptible to Ceftriaxone and Cefepime in around 83% instances according to hospital's annual antibiogram report. Almost similar susceptible patterns were also reported for *Streptococcus pyogenes* and *Haemophilus influenzae* for Cephalosporin antibiotics. These susceptibility patterns showed that initiating empirically prescribed Ceftriaxone or Cefepime antibiotic therapy can be helpful in reducing the incidences of secondary infections as a major complication associated with increased mortality and morbidity of Influenza-A (H1N1)pdm09 infection patients hospitalized due to severity of Influenza infection. This consideration can be of mere importance especially in cases of elderly patients and people who had not received pneumococcal and Influenza vaccine as per recommendation.

During Influenza-A (H1N1) pandemic 2009, bacterial pneumonia was found in 4–33% of hospitalized or critically sick patients (Investigators, 2009, Martín-Loeches, Sanchez-Corral *et al*., 2011, Morens, Taubenberger *et al*., 2008, Randolph, Vaughn *et al*., 2011, Rice, Rubinson *et al*., 2012). All previous pandemics interposed to excess mortality partially because of secondary bacterial infections (Morens, Taubenberger *et al*., 2008). Three studies which excluded participants based on antibiotic usage, reported bacterial secondary infection at the rates of 12.2%, 26.7%, and 46.6% (Ahn, Kim *et al*., 2011, Cuquemelle, Soulis *et al*., 2011, Falsey, Becker *et al*., 2013). Neuraminidase inhibitor with an antibiotic should be considered for high risk Influenza infected patients i.e. elderly and those with chronic diseases (McCullers, 2004). Observational studies suggest that timely Oseltamivir administration can decrease the possibility of progression to pneumonia. Even though, revealed in animal model of consequent infection, it is uncertain the degree to which NAIs reduce the risk of bacterial pneumonia in Influenza infected humans

It has been implied in an analytical study that incorporation of antibiotic with immunotherapy or antiviral agent can improve the probabilities of successful treatment by 200% (Smith, 2018). In current study, the patients who were initiated on combination therapy (Group-2 patients) soon after the confirmed diagnosis of Influenza-A (H1N1)pdm09 were found to recovered more rapidly and completely from severe illness and suffered less severe complications such as requirement of respiratory support, less incidences of severe bacterial secondary infections, fewer cases of multiple organ dysfunction etc which were ultimately associated with rapid recovery of severe illness. This rapid recovery from severe illness in Group-2 patients was also deflected in average length of hospitalization days which were found to be statistically significant less for Group-2 patients with 5.43±1.23 days as compare to Group-1 patients whom average length of hospitalization was around 36-48 hours longer. Even the patients who required respiratory support, the average length of days on which patient was put on respiratory support was statistically significant less for Group-2 patients with 3.6 ± 1.21 days in comparison to 5.4 ± 1.30 days of Group-1 patients.

Table 1: Demographic characteristics and clinical features of study participants

	Group-1 (Oseltamivir Alone)	Group-2 (Oseltamivir+Antibiotic)	P-Value
	Total enrolled patients		
No. of patients	227	116	
	Gender		0.905
Male	110 (48.5%)	61 (52.6%)	
Female	117 (51.5%)	55 (47.4%)	
	Age (years)		0.13
Mean	55.86	58.65	
SD	13.32	16.09	
Range	26-81	23-85	
	Weight (kg)		0.25
Mean	78.07	79.98	
SD	12.78	13.96	
	Influenza vaccination		0.551
Yes	34 (15%)	15 (12.9%)	
No	193 (85%)	101 (87.1%)	
	Pneumococcal vaccine		0.65
Yes	26 (11.4%)	11 (9.5%)	
No	201 (88.6%)	105 (90.5%)	
	Comorbidities		
Asthma	61 (26.8%)	32 (27.6%)	
Hypertension	70 (30.8%)	36 (31.1%)	
Cardiovascular	24 (10.6%)	14 (12.1%)	
Diabetes	56 (24.7%)	33 (28.4%)	
Renal	32 (14.1%)	20 (17.2%)	
	Haematological parameters at admission		
RBCs	4.31±0.54	4.81±0.70	
WBCs	11.13±3.5	11.5±2.4	
Neutrophils	6.5±2.65	6.37±3.59	
Platelets	245±56.74	241±71.14	
	Biochemistry parameters		
Sodium	137±3.45	135.37±3.01	
Potassium	3.93±0.56	4.15±0.62	
BUN	5.13±2.63	4.81±2.46	

Where; SD= Standard Deviation, RBCs= Red Blood Cells, WBC= White Blood Cells, BUN= Blood Urea Nitrogen

Table 2: Comparison of clinical outcomes for both treatment groups

	Group 1 (Oseltamivir Alone)	Group 2 (Oseltamivir + Antibiotic)	P-value
	Total enrolled patients		
No. of patients	227	116	
	Incidences of secondary infections		
No. of patients	53 (23.4%)	12 (10.3%)	0.001
	Length of stay in hospital		
Mean days ± SD	6.58±2.09	5.43±1.23	<0.0001
	Need of Respiratory support		
Incidences	87 (38.3%)	11 (9.5%)	0.001
	Need of respiratory support days		
Mean days ± SD	5.4 ± 1.30	3.6 ± 1.21	0.004
	Patients requiring ICU admission		
No. of patients	64 (28.2%)	07 (18.1%)	0.04
	No. Of days in ICU		
Mean days ± SD	7.71± 2.1	3.57 ± 1.54	0.06
	Multiple organ failure		
No. of patients	37 (17.4%)	07 (6.7%)	0.03

Abbreviations: ICU=Intensive Care Unit

Table 3: Microbiological isolates for secondary bacterial infections

Microbiological Organism	Group-1 (Oseltamivir Alone)	Group-2 (Oseltamivir + Antibiotic)	P-value
	Incidences of secondary infections		
No. of patients	53	12	0.001
	Microbiological isolates- secondary infections		
Streptococcus pneumoniae	12 (22.6%)	0	
Streptococcus pyogenes	2 (3.77%)	0	
Streptococcus agalactiae	0	0	
Staphylococcus aureus (MSSA)	7 (13.2%)	1 (8.3%)	
Staphylococcus aureus (MRSA)	3 (5.67%)	2 (16.7%)	
Neisseria meningitidis	3 (5.67%)	0	
Klebsiella pneumonia	3 (5.67%)	2 (16.7%)	
Escherichia coli	2 (3.77%)	1 (8.3%)	
Pseudomonas aeruginosa	2 (3.77%)	1 (8.3%)	
Acinetobacter sp.	2 (3.77%)	1 (8.3%)	
Haemophilus influenzae	4 (7.54%)	0	
Proteus mirabilis	2 (3.77%)	0	
Chlaymydia pneumoniae	3 (5.67%)	2 (16.7%)	
Mycoplasma pneumoniae	8 (15.1%)	2 (16.7%)	

Table 4: Characteristics of patients suffered from secondary bacterial infection as associated complication of Influenza-A (H1N1) pdm09 infection

	Secondary infections	
	Group-1	Group-2
	N=53	N=12
	Age of Patients	
>65 years, Yes (%)	14 (26.4%)	4 (33.3%)
>50 <65years, Yes (%)	22 (41.5%)	8 (67.7%)
	Incidences of Bacterial Pneumonia	
No. of Patients, Yes (%)	38 (71.6%)	6 (50%)
	Incidences of Bacterial Sepsis	
No. of Patients, Yes (%)	15 (28.3%)	6 (50%)
	Influenza Vaccination history	
No. of patients, Yes (%)	5 (9.4%)	0
	Pneumococcal Vaccination history	
No. of patients, Yes (%)	0	0
	Comorbidities	
Obesity	31 (58.4%)	5 (41.6%)
Diabetes	20 (37.7%)	4 (33.3%)
Acute Kidney Injury	13 (24.5%)	2 (16.7%)
Chronic Respiratory disease	24 (54.7%)	3 (25%)
Cardiovascular disease	14 (23%)	2 (16.7%)

Table 5: Summarized comparisons of different cephalosporin antibiotics in combination with Oseltamivir- Group 2 patients (n=116)

	Cefuroxime	Ceftriaxone	Cefepime
	No. of patients given		
	31	47	38
	Secondary Infections- Bacterial Pneumonia (n=6)		
No. of Patients, Yes (%)	4 (66.7%)	1 (16.7%)	1 (16.7%)
	Secondary infections- Bacterial Sepsis (n=6)		
No. of Patients, Yes (%)	3 (50%)	1 (16.7%)	2 (33.3%)
	Need of respiratory Support (n=11)		
No. of Patients, Yes (%)	6 (54.5%)	1 (9.09%)	4 (36.4%)
	Need to shift to Intensive Care Unit (n=7)		
No. of Patients, Yes (%)	4 (57.1%)	1 (14.3%)	2 (28.6%)

In a study conducted by Shilet *et al*., (2010) Oseltamivir was prescribed for a small percentage (21%) of patients with Influenza; one-half of these patients continued to receive antibiotics and the spectrum of antibiotics used (Fluoroquinolones, Cephalosporins, and Macrolides) further suggest that clinicians harboured concerns for concomitant bacterial pneumonia (Shiley, Lautenbach *et al*., 2010). However, it was observed in our study that three Cephalosporins used were Cefuroxime, Ceftriaxone and Cefepime among patients who were given combination treatment with Oseltamivir (group 2 patients). Among Cephalosporins, Cefuroxime combination with Oseltamivir was found to be least efficacious and effective in preventing patients from secondary bacterial infections, need of respiratory support and ICU admission while Ceftriaxone and Cefepime were found to be almost equally effective in reducing and preventing complications associated with severe Influenza-A (H1N1)pdm09 infection.

Differentiating viral from bacterial infection remains a challenge for clinicians. This diagnostic uncertainty has contributed to a widely recognized overuse of antibiotics in patients with viral illness (Gonzales, Bartlett *et al*., 2001, Metlay, Camargo Jr *et al*., 2007). A potential limitation of current study is that the Oseltamivir combination with other antibiotics has not been studied. There is a need to develop proactive treatment strategies of existing antiviral in combination with other drugs for the prevention of complications associated with viral Influenza infection especially for late diagnosis and high risk patents.

CONCLUSION

In severe Influenza infection hospitalized patients diagnosed with Influenza-A (H1N1)pdm09 strain, early initiation of empirically prescribed Cephalosporin antibiotic in combination with neuraminidase inhibitor antiviral drug (Oseltamivir) has shown positive outcomes with reduced incidences of secondary bacterial infections, shorter length of stay in hospital, fewer incidences of respiratory support and admission to ICU which are usual complications associated with severe Influenza infection especially in unvaccinated and elderly patients who are more prone to severe complications in case of Influenza infection.

REFERENCES

Ahn S, Kim WY, Kim SH, Hong S, Lim CM, Koh Y, Lim KS and Kim W (2011). Role of procalcitonin and C - reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia. *Influenza. Other. Resp.,* **5**(6): 398-403.

America IDSo Influenza H1N1: frontline questions and expert opinion answers. Arlington, VA: Infectious Diseases Society of America; 2009.

Campigotto A and Mubareka S (2015). Influenza-associated bacterial pneumonia; Managing and controlling infection on two fronts. *Expert. Rev. Anti-Infe.,* **13**(1): 55-68.

Chertow DS and Memoli MJ (2013). Bacterial coinfection in influenza: A grand rounds review. *Jama* **309**(3): 275-282.

Chong CP and Street PR (2008). Pneumonia in the elderly: A review of the epidemiology, pathogenesis, microbiology, and clinical features. *South. Med. J.*, **101**(11): 1141-1145

Cuquemelle E, Soulis F, Villers D, Roche-Campo F, Somohano CA, Fartoukh M, Kouatchet A, Mourvillier B, Dellamonica J and Picard W (2011). Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *J. Intensive. Care Med.,* **37**(5): 796-800.

Davey S (1999). World Health Organization report on infectious diseases. Removing obstacles to healthy development.

Engelmann I, Dubos F, Lobert P-E, Houssin C, Degas V, Sardet A, Decoster A, Dewilde A, Martinot A and Hober D (2015). Diagnosis of viral infections using myxovirus resistance protein A (MxA). *Pediatrics* **135**(4): e985-e993.

Falsey AR, Becker KL, Swinburne AJ, Nylen ES, Formica MA, Hennessey PA, Criddle MM, Peterson DR, Baran A and Walsh EE (2013). Bacterial complications of respiratory tract viral illness: A comprehensive evaluation. *J. Infect.,* **208**(3): 432-441.

Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman JR and Sande MA (2001). Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: Background, specific aims and methods. *Ann. Intern. Med.,* **134**(6): 479-486.

Investigators AI (2009). Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *New England Journal of Medicine* **361**(20): 1925-1934.

Janssens JP and Krause KH (2004). Pneumonia in the very old. *Lancet. Infect. Dis.,* **4**(2): 112-124.

Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH and Dugas A (2016). The frequency of influenza and bacterial coinfection: a systematic review and meta analysis. *Influenza. Other. Resp.,* **10**(5): 394-403.

Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, Cavalieri ML, Guglielmo MC, Areso MS and Gilligan T (2010). Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1)pdm09 in Argentina. *N. Engl. J. Med.,* **362**(1): 45-55.

Lim WS (2007). Pandemic flu: Clinical management of patients with an influenza-like illness during an influenza pandemic. *Thorax* **62**(suppl 1): 1-46.

Martín-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, Albaya A, Cerdá E, Catalán RM and Luque P (2011). Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A (H1N1)pdm09 virus. *Chest* **139**(3): 555-562.

McCullers JA (2004). Effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza. *J. Infec.,* **190**(3): 519-526.

Metlay JP, Camargo Jr CA, MacKenzie T, McCulloch C, Maselli J, Levin SK, Kersey A, Gonzales R and Investigators I (2007). Cluster-randomized trial to improve antibiotic use for adults with acute respiratory infections treated in emergency departments. *Ann. Emerg. Med.,* **50**(3): 221-230.

Morens DM, Taubenberger JK and Fauci AS (2008). Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J. Infec.,* **198**(7): 962-970.

Ng H, Narasaraju T, Phoon M, Sim M, Seet J and Chow VT (2012). Doxycycline treatment attenuates acute lung injury in mice infected with virulent influenza H3N2 virus: involvement of matrix metalloproteinases. *Exp. Mol. Pathol.,* **92**(3): 287-295.

Pasman L (2012). The complication of coinfection. *Yale. J. Biol. Med.,* **85**(1): 127.

Purcell K and Fergie J (2002). Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections. *Arch. Pediat. Adol. Med.,* **156**(4): 322-324.

Purcell K and Fergie J (2004). Concurrent serious bacterial infections in 912 infants and children hospitalized for treatment of respiratory syncytial virus lower respiratory tract infection. *Pediatr. Infect. Dis. J.,* **23**(3): 267-269.

Randolph AG, Vaughn F, Sullivan R, Rubinson L, Thompson BT, Yoon G, Smoot E, Rice TW, Loftis LL and Helfaer M (2011). Critically ill children during the 2009-2010 influenza pandemic in the United States. *Pediatrics,* **128**(6): e1450-e1458.

Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller III RR, Higgs E, Randolph AG, Smoot BE and Thompson BT (2012). Critical illness from 2009 pandemic influenza A (H1N1)pdm09 virus and bacterial co-infection in the United States. *Crit. Care Med.,* **40**(5): 1487.

Shiley KT, Lautenbach E and Lee I (2010). The use of antimicrobial agents after diagnosis of viral respiratory tract infections in hospitalized adults: antibiotics or anxiolytics? *Infect. Control Hosp. Epidemiol.,* **31**(11): 1177-1183.

Smith AM (2018). Host pathogen kinetics during influenza infection and coinfection: insights from predictive modeling. *Immunol. Rev.,* **285**(1): 97-112.

Smith AM and McCullers JA (2014). Secondary bacterial infections in influenza virus infection pathogenesis. *Curr. Top. Microbiol. Immunol.,* **385**: pp.327-356.

Stupka JE, Mortensen EM, Anzueto A and Restrepo MI (2009). Community-acquired pneumonia in elderly patients. *J. Aging Health.,* **5**(6): 763-774.